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RTP801 is elevated in Parkinson brain substantia nigral neurons and mediates death in cellular models of Parkinson's disease by a mechanism involving mammalian target of rapamycin inactivation.

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The molecules underlying neuron loss in Parkinson's disease (PD) are essentially unknown, and current therapies focus on diminishing symptoms rather than preventing neuron death. We identified RTP801 as a gene whose transcripts were highly induced in a cellular model of PD in which death of neuronal catecholaminergic PC12 cells was triggered by the PD mimetic 6-OHDA. Here, we find that RTP801 protein is also induced in this and additional cellular and animal PD models. To assess the relevance of these observations to PD, we used immunohistochemistry to compare RTP801 expression in postmortem brains from PD and control patients. For all PD brains examined, expression was highly elevated within neuromelanin-containing neurons of the substantia nigra but not in cerebellar neurons. Evaluation of the potential role of RTP801 induction in our cellular model revealed that RTP801 overexpression is sufficient to promote death but does not further elevate death caused by 6-OHDA. Furthermore, RTP801 induction is requisite for death in our cellular PD models and in 6-OHDA-treated cultured sympathetic neurons in that its knockdown by short hairpin RNAs (shRNAs) is protective. The mechanism by which 6-OHDA and RTP801 induce neuron death appears to involve repression of mammalian target of rapamycin (mTOR) kinase activity, and such death is inhibited by shRNAs targeting TSC2 (tuberous sclerosis complex), a protein with which RTP801 interacts to block mTOR activation. Our findings thus suggest that the elevation of RTP801 we detect in PD substantia nigral neurons may mediate their degeneration and death and that RTP801 and its signaling cascade may be novel potential therapeutic targets for the disease.

Publication Types:
- Research Support, N.I.H., Extramural
- Research Support, Non-U.S. Gov't

PMID: 17005863 [PubMed - indexed for MEDLINE]